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DuRvalumab with chEmotherapy as first line treAtment in advanced pleural Mesothelioma - A phase 3 Randomised trial (DREAM3R).

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Abstract

Introduction

There is a strong theoretical rationale for combining checkpoint blockade with cytotoxic chemotherapy in pleural mesothelioma and other cancers. Two recent single-arm, phase 2 trials (DREAM and PrE0505) combining the PD-L1 inhibitor durvalumab with standard first line chemotherapy exceeded pre-specified safety and activity criteria to proceed to a phase 3 confirmatory trial to assess this combination.

Methods and analysis

This multicentre open-label randomised trial will recruit 480 treatment-naïve adults with advanced pleural mesothelioma, randomised (2:1) to either 3-weekly durvalumab 1500mg plus 3-weekly doublet chemotherapy (cisplatin 75mg/m^2 or carboplatin AUC 5 and pemetrexed 500mg/m^2) 4-6 cycles, followed by 4-weekly durvalumab 1500mg until disease progression, unacceptable toxicity or patient withdrawal; OR doublet chemotherapy alone for 4-6 cycles, followed by observation. The target accrual time is 27 months, with follow up for an additional 24 months. This provides over 85% power if the true hazard ratio for overall survival (OS) is 0.70, with 2-sided alpha of 0.05, assuming a median OS of 15 months in the control group. Randomisation is stratified by age (18-70 years vs. > 70), sex, histology (epithelioid vs. non-epithelioid), platinum agent (cisplatin vs. carboplatin) and region (USA vs. Australia/ New Zealand vs. Other). The primary endpoint is OS. Secondary endpoints include progression-free survival, objective tumour response (by mRECIST 1.1 and iRECIST), adverse events, health-related quality of life, and healthcare resource use. Tertiary

correlative objectives are to explore and validate potential prognostic and/or predictive biomarkers (including features identified in the DREAM and PrE0505 studies, PD-L1 expression, tumour mutational burden, genomic characteristics, and HLA subtypes) in tissue and serial blood samples. An imaging databank will be assembled for validation of radiological measures of response, and studies of possible radiomic biomarkers in mesothelioma.

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Ethics and dissemination

The protocol was approved by human research ethics review committees for all participating sites. Results will be disseminated in peer-reviewed journals and at scientific conferences.

Drug Supply

AstraZeneca

Protocol version

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Strengths and limitations of this study

- International, open-labelled, randomised phase 3 trial of immunotherapy and chemotherapy in first line treatment of pleural mesothelioma.
- Strong biological rationale and earlier phase clinical data
- Extensive translational science biospecimen collection and plans
- The treatment landscape for mesothelioma is evolving with the demonstration of efficacy of first line dual immunotherapy

Introduction

The incidence of pleural mesothelioma continues to rise worldwide, particularly in Asia, despite bans on using asbestos in many countries.[1] The annual incidence rates in the UK, Australia and the USA in 2019-2021 were 6.8, 4.2 and 1.51 per 100,000 people, respectively.[2-4] Once diagnosed, mesothelioma is generally incurable and has a median survival of less than one year. Systemic treatment with palliative intent is the only option for the majority of patients.[5-7] Hundreds of thousands of people worldwide will require systemic therapy for mesothelioma in coming decades.

Current Treatment Options in Mesothelioma

Since 2003, the standard first line chemotherapy for advanced unresectable pleural mesothelioma has been platinum-based chemotherapy with 4-6 cycles of cisplatin or carboplatin, with Pemetrexed. This provides a median survival benefit of approximately 3 months over cisplatin alone in the pivotal trail, and benefits in patient-reported outcomes.[5-8] More recently, the combination of chemotherapy with bevacizumab, a vascular endothelial growth factor inhibitor, demonstrated an additional median survival benefit of 2 months.[9] However, this combination was not approved by the US FDA and most other regulatory bodies. Addition of the multi-targeted tyrosine kinase inhibitor nintedanib to chemotherapy also resulted in a progression-free survival (PFS) benefit in a randomised phase 2 trial, but a subsequent randomised phase 3 trial was negative.[10] The majority of patients who respond to first line therapy experience tumor progression soon after it is completed. Thus, there has been a strong unmet clinical need to improve first line systemic therapy in mesothelioma.

Rationale for Immunotherapy in Mesothelioma

The activity of immunotherapy in mesothelioma has been demonstrated in second and subsequent line studies.[11-18] In earlier studies, outcomes with single agent immunotherapy varied with the population and setting, but clearly indicated activity. The recent randomised phase 3 PROMISE trial showed similar outcomes with single agent pembrolizumab versus

single agent chemotherapy when used as second line treatment.[17] However, nivolumab provided benefits in progression-free and overall survival in comparison with best supportive care in the second- or subsequent-line setting. Trials of dual immunotherapy as second line treatment have shown longer PFS than single agent immunotherapy in the MAPS-2[14] and NIBIT-MESO-1[19] studies, however these observations require further validation in larger trials with OS as the primary end point to outweigh the toxicities of dual immunotherapy.

The recently reported results of the CheckMate-743 phase 3 randomised trial of dual immunotherapy with ipilimumab and nivolumab as first line chemotherapy showed a significant improvement in OS when compared with a platinum-based doublet (HR 0.74; 95% CI 0.60-0.91; p=0.002).[20] However, the OS benefit was observed predominantly in the subgroup with non-epithelioid histology (25% of participants), rather than among the more common subgroup with epithelioid histology (75% of participants). There was also no benefit observed in PFS or objective response rate (ORR) compared with chemotherapy.

First line combination of immunotherapy and chemotherapy

Two recent single-arm first line phase 2 trials combining durvalumab with platinum-based doublet chemotherapy showed encouraging activity and acceptable safety in advanced mesothelioma of all subtypes.[21,22] The Australian DREAM trial of 54 participants exceeded its pre-specified target with a 6-month PFS rate of 57%.[21] The ORR was 48%, median PFS was 7 months by mRECIST and iRECIST; median OS was 18 months In the US-based PrECOG 0505 trial of 55 participants, the median OS was 20.4 months, 12-month OS rate was 70% (95% CI 56-81), ORR was 56%, 6-month PFS rate was 69.1% and median PFS was 7 months.[22]

DREAM3R was designed and developed before results from CheckMate-743 were available. The positive results of CheckMate-743 strengthen the strong rationale for DREAM3R. The OS benefit in Checkmate-743 was uncertain in the subgroup with epithelioid histology, and

not evident in the subgroup with tumours that did not express PD-L1. Results of translational research studies to identify those more likely to benefit are pending.

Given the favourable OS and PFS data from the DREAM and PrE0505 trials, DREAM3R aims to determine the effectiveness of adding durvalumab to cisplatin/carboplatin and pemetrexed. Our primary hypothesis is that the addition of durvalumab will prolong OS in comparison with platinum and pemetrexed alone.

Methods and analyses

Trial design

The DREAM3R trial is an international, open label, randomised (2:1), multi-centre, phase 3 trial. The planned study sites include 29 in Australia, 1 in New Zealand and 30 from the USA.

Participants are randomised in a ratio of 2:1 to either durvalumab + chemotherapy or chemotherapy alone, by a central computerized system that uses permuted blocks to stratify for (see Figure 1):

1. Age (18-70 years vs older than 70)
2. Sex (male vs female)
3. Histology (epithelioid vs non-epithelioid)
4. Region (Australia/New Zealand vs USA vs other)
5. Platinum agent (cisplatin vs carboplatin)

Inclusion criteria

Participants who fulfil these criteria are considered eligible:

- Adults with a histological diagnosis of pleural mesothelioma of any histological type, that is not amenable to curative surgical resection. Histological diagnosis requires tumour tissue from an open biopsy, or a core biopsy with a needle of 19 gauge or wider.
- Measurable disease per mRECIST 1.1 for pleural mesothelioma
- No prior radiotherapy to measurable disease

- Eastern Cooperative Oncology Group (ECOG) score 0 to 1
- Tumour tissue (FFPE) available from diagnostic biopsy for PD-L1
- Adequate blood tests (done within 14 days prior to randomisation) and with values within the ranges specified below. Blood transfusions are permissible if completed at least 7 days prior to treatment start.
    - Haemoglobin ≥ 9.0 g/L
    - Absolute neutrophil count ≥ 1.5 x 10^9/L
    - Platelets ≥ 100 x 10^9/L
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (except participants with Gilbert's Syndrome, who are eligible with bilirubin ≤ 2.5 ULN)
    - Alanine transaminase ≤ 2.5 x upper limit of normal (ULN), unless liver metastases or invasion are present, in which case it must be ≤ 5 x ULN
    - Aspartate aminotransferase ≤ 2.5 x ULN, unless liver metastases or invasion are present, in which case it must be ≤ 5 x ULN
    - Creatinine clearance (CrCl) ≥ 45 mL/min (per Cockcroft-Gault formula)
- Life expectancy at least 12 weeks
- Women of childbearing potential must use a reliable means of contraception during treatment and for at least 90 days thereafter. Breastfeeding is not permissible during or for at least 90 days after the final study treatment. Men must have been surgically sterilised or use a (double if required) barrier method of contraception if they are sexually active with a woman of child bearing potential

- Evidence of post-menopausal status or negative serum pregnancy test for female pre-menopausal participants. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause.

Exclusion criteria

Participants who meet the following criteria are considered ineligible

- Received prior chemotherapy, immune checkpoint inhibitor or other systemic anti-cancer therapy for pleural mesothelioma
- Diagnosis on cytology or fine needle aspiration only
- Contraindication for immune checkpoint inhibitor such as active or documented autoimmune or inflammatory disorder
- Any condition requiring systemic treatment with corticosteroids (>10mg daily prednisone or equivalent) or other immunosuppressive medications within 28 days
- Symptomatic or uncontrolled brain or leptomeningeal metastases
- Hearing loss or peripheral neuropathy considered by the investigators to contraindicate cisplatin administration
- History of allergy or hypersensitivity to investigational product, cisplatin, pemetrexed or any excipient.
- No other malignancy that requires active treatment. Participants with a past history of adequately treated carcinoma in situ, non-melanoma skin cancer or lentigo maligna without evidence of disease or superficial transitional cell carcinoma of the bladder are eligible.
- Current treatment or treatment within the last 12 months with any investigational anti-cancer products.
- Concurrent enrolment in another clinical trial testing an anticancer treatment.

- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive cardiac failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, active peptic ulcer disease or gastritis, serious chronic gastrointestinal conditions associated with diarrhoea, active bleeding diatheses.
- Hepatitis B, hepatitis C or human immunodeficiency virus (HIV). Exceptions include past or resolved Hepatitis B (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) and participants positive for hepatitis C (HCV) antibody if polymerase chain reaction is negative for HCV RNA. HIV testing is not required in absence of clinical suspicion of HIV.
- Known history of primary immunodeficiency, allogeneic organ transplant, pneumonitis or active tuberculosis.
- Receipt of live attenuated vaccination within 30 days prior to enrolment or within 30 days of receiving durvalumab.

Study objectives

The primary objective of DREAM3R trial is to determine the effects of adding durvalumab on OS. Secondary objectives are to determine effects on

PFS (by mRECIST 1.1 for pleural mesothelioma and iRECIST)

Objective tumour response [(OTR) by mRECIST 1.1 for pleural mesothelioma and iRECIST]

Adverse events according to Common Terminology Criteria (CTCAE v5.0)

Health-related quality of life (HRQL, EORTC QLQ-C30, QLQ LC-29, EQ-5D-5L)

Healthcare resource use

Incremental cost-effectiveness

Tertiary/ correlative objectives are

To explore and validate potential prognostic or predictive biomarkers of clinical outcomes, (including but not limited to candidates identified in the phase II DREAM and PrE0505 studies, PD-L1 expression, HLA type, T cell tumour infiltration, T cell receptor repertoire, tumour mutational burden and gene signatures)

To collect an imaging databank for future validation of radiological response metrics in pleural mesothelioma

Treatment arms

Investigational arm (Arm A)

Standard doublet chemotherapy + durvalumab, followed by durvalumab maintenance (see Table 1)

Cisplatin/ carboplatin and pemetrexed are administered before durvalumab. Durvalumab is administered immediately following or during the final hydration IV fluid bag for cisplatin/ carboplatin administration.

Chemotherapy is continued for a maximum of 6 cycles in the absence of prohibitibve toxicity (e.g. cumulative neuropathy, hearing impairment, kidney impairment). However, after the patient has completed 4 cycles it is up to the judgement of the site investigator whether to complete all 6 cycles.

Durvalumab is continued if chemotherapy is stopped prior to completion of 6 cycles in participants with tumors that are stable or responding to treatment.

For participants entering into the maintenance stage, the first dose of durvalumab should commence 3 weeks after the last dose of chemo-durvalumab. Subsequent treatments with durvalumab will continue at 1500 mg on Day 1 of a **4-weekly cycle** in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or other reasons for discontinuation.

Control arm (Arm B)

Standard doublet chemotherapy followed by close observation (see Table 2).

In both arms

Carboplatin AUC 5 is the initial platinum agent of choice in participants with an estimated creatinine clearance 45 to 59 mL/min, or those with clinically reported hearing loss. Carboplatin or cisplatin may be chosen for other participants at the discretion of investigators. Participants experiencing unacceptable cisplatin toxicities may be treated subsequently with carboplatin AUC 5 every 3 weeks. Regimens for antiemetic and hydration are as per local institutional guidelines.

Trial oversight and monitoring

DREAM3R is an investigator-initiated, academic trial, conducted as a collaboration between the Thoracic Oncology Group of Australasia (TOGA), the NHMRC Clinical Trials Centre at the University of Sydney, and PrECOG, a non-profit research company that focuses on cancer clinical trials. The University of Sydney is the sponsor in Australia and New Zealand, PrECOG is the sponsor in USA. This international study will be conducted through a number of regional coordinating centres, each responsible for their own ethics and regulatory approvals, regional monitoring, medical oversight and facilitation of data collection and query resolution. The NHMRC Clinical Trials Centre will be responsible for study coordination, data acquisition, management, and statistical analysis.

The trial will be monitored by an Independent Safety and Data Monitoring Committee (ISDMC) approximately every 6 months. The ISDMC will advise the Trial Monitoring Committee (TMC) regarding safety, specified matters related to the integrity and potential conclusions of trial data, and the appropriateness of continued trial conduct.

The International Trial Steering Committee (ITSC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). The ITSC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on safety monitoring or other information.

Each regional coordinating centre will constitute its own regional TMC, including a clinical lead and coordinating centre lead who will represent the region on the ITSC.

Changes and amendments to the protocol can only be initiated and made by the ITSC. Approval of protocol amendments by the Institutional Human Research Ethics Committees is required prior to their implementation.

Patient and Public Involvement

Patient and members of the public were involved at several stages of the trial, including the design, management, and conduct of the trial. We received input from mesothelioma patients in the design of the trial materials and management oversight through membership of the trial steering committee. We carefully assessed the burden of the trial interventions on patients. We intend to disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

Statistical considerations

Sample size

Enrolment of 480 participants (randomised 2:1) over 27 months and followed for at least another 24 months, provides >85% power assuming a true hazard ratio of 0.70, a median survival of 15 months in the control group and a median survival of 21.4 months in the durvalumab group. The alternate hypothesis (difference) will be tested against the null

hypothesis (no difference) with a 2-sided alpha of 0.05. There is an allowance for non-compliance with assigned treatment of 6%.

A single interim analysis will be conducted according to the alpha spending approach using an O'Brien-Fleming boundary. The interim analysis will be conducted at least 6 months after the completion of recruitment and having observed 50% events required for the final analysis. The exact boundary will be computed prior to the analysis according to the percentage of information observed. For example, at exactly 50% information (176 events) the analysis would use alpha=0.0031 and declare a significant result if the observed HR<0.64. The final analysis (352 events) would then be based on with alpha 0.049 and have power of 85% if the true HR was 0.70.

Statistical analysis

All randomised participants will be included in the analysis. With the exception of safety data, all analyses will be conducted on an intention to treat basis (safety analysis will be reported by treatment as received within all participants who received any study treatment). 95% confidence intervals (CI) will be reported for all relevant estimates. A statistical analysis plan will be prepared prior to the final analysis. This document will contain additional detail on the methods described here.

The primary endpoint of the study is OS, defined as the time from randomisation to the date of death due to any cause. Participants who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last known alive date. All randomised participants will be included in the analysis of OS. Kaplan-Meier estimates will be computed for both groups. CI for the median survival will be computed by the method of Brookmeyer and Crowley. In the primary analysis, the two treatment arms will be compared using the log-rank test stratified by stratification factors. Cox regression modelling will be used to estimate the treatment effect both on an unadjusted basis and adjusted for stratification variables.

PFS is a secondary endpoint of this study, defined as the time from randomisation to the date of the first documented disease progression (based on mRECIST and iRECIST) or death due to any cause. A patient who stops treatment with study drug and goes on to receive alternative therapy for pleural mesothelioma, prior to documentation of disease progression, will be censored on the date alternative therapy began. If a patient has not progressed or received alternative therapy, PFS will be censored on the date of the last disease assessment. All randomised participants will be included in the analysis of PFS. All analyses for OS will be similarly performed for PFS.

OTR rate is defined as the proportion of participants with a documented complete response, partial response (CR + PR) based on iRECIST criteria. Results for tumor-related endpoints (PFS and ORR) based on iRECIST will be considered exploratory. The primary estimate of OTRR will be based on all participants randomised, and compared using Cochran-Mantel-Haenszel test stratified by stratification factors. Quality of life analysis will be conducted with appropriate methods to account for repeated measures.

An exploratory analysis of biomarkers (from tissue, serial bloods) and their associations with clinical endpoints will be conducted. These exploratory analyses will be descriptive/graphical in nature, and are designed to generate new hypotheses to be tested in future clinical studies. Where parameters of immune response are measured, continuous variables will be summarized with means and standard deviations. Dichotomous and categorical variables will be summarized using proportions with exact 95% confidence intervals and counts, respectively. These summaries will be computed for each treated patient at multiple time points, before and after treatment administration, as indicated in the study schema. Plots will be used to show the changes in immune response over time for each individual. For each patient, comparisons in the pre- and post-durvalumab responses will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and

McNemars test for dichotomous or categorical variables. Associations between immune responses will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g. correlations, $\chi 2$ tests).

Ethics and Dissemination

The study will be conducted according to the ICH Guideline for Good Clinical Practice Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6(R2) dated 9 November 2016, the principles laid down by the World Medical Association in the Declaration of Helsinki 2013 and pertinent regional regulations.

Trial status

Patient enrolment commenced in February 2021 at Sir Charles Gardiner Hospital, Perth, Australia. As of the 15th September 2021, 41 of the 60 planned sites have opened to recruitment and 45 participants have been randomised.

Word count: 2989 (max 3500)

Figure

Figure 1: Schema for DREAM3R

Tables

Table 1: Investigational arm treatment

Agent (s)	Dose	Route	Duration	Schedule	Frequency
Cisplatin OR Carboplatin	75 mg/m^2 OR AUC 5	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Pemetrexed	500 mg/m^2	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Durvalumab	1500 mg	IV	60 minutes	Day 1 each cycle	Every 3 weeks
Followed by Maintenance					
Durvalumab	1500 mg	IV	60 minutes	Day 1 each cycle	**Every 4 weeks** Until disease progression/ unacceptable toxicity/ withdrawal of consent

Table 2: Control arm treatment

Agent (s)	Dose	Route	Duration	Schedule	Frequency
Cisplatin OR Carboplatin	75 mg/m^2 OR AUC 5	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Pemetrexed	500 mg/m^2	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Followed by					
Close observation per standard of care					

Conflict of interest

Dr Sun, Dr Brown, Dr Cook, Dr Yip, Ms Ford, Ms Fitzpatrick, Ms Bricker, Ms Cummins have nothing to disclose.

Dr Kok reports grants and fees from AstraZeneca and Pfizer, she is a consultant/ advisory board member of MSD, outside the submitted work;

Dr. Forde reports grants and fees from AstraZeneca, BMS, Corvus, Novartis, Kyowa; he is a consultant/ advisory board member of Amgen, AstraZeneca, BMS, Novartis, Janssen, Iteos, Mirati, Sanofi; he is a Data Safety Monitoring Board member of Polaris, Flame, outside the submitted work;

Dr Hughes is a consultant/ advisory board member of MSD, BMS, Roche, Pfizer, AstraZeneca, Eisai, Takeda; his institution received grants from Amgen, outside the submitted work;

Dr Ramalingam reports grants and fees from Amgen, AstraZeneca, Genmab, Eisai, Lilly, Roche, Merck, Takeda and GSK; he is a Data Safety Monitoring Board member of Jansen; a member of Board for Gergia Society of Oncology and IASLC; his institution received grants from AstraZenca, Amgen, BMS, Merck, Genmab, Takeda, Advaxis and Pfizer, outside the submitted work;

Dr. Lesterhuis reports grants and fees from Douglas Pharmaceuticals, and patents relating to immune checkpoint therapy, unrelated to this study, outside the submitted work;

Dr O'Byrne has received advisory board and/or speaker bureau and/or meeting travel/registration support from BMS, MSD, LillyOncology, Boehringer-Ingelheim, Pfizer, Novartis, Roche-Genentech,Teva, Mundipharma, Astrazeneca, Janssen, Natera and TriStar. He is a board member and stock holder for Carpe Vitae Pharmaceuticals and a stock holder for RepLuca Pharmaceuticals and DGC Diagnostics and holds patents for novel therapeutics and diagnostic tests, outside the submitted work;

Dr. Pavlakis reports grants and fees from Boehringer Ingelheim, Bayer, Novartis, Pfizer, Roche, Takeda and Ipsen; he is an advisory board member of Boehringer Ingelheim, MSD, Merck, BMS, Astra Zeneca, Takeda, Pfizer and Roche; his institution received grants from Bayer, Pfizer and Roche, outside the submitted work;

Dr Brahmer reports grants and fees from AstraZeneca, BMS, Genentech/Roche, Merck, RAPT Therapeutics, Revolution Medicines, Amgen, Eli Lilly, GlaxoSmithKline, Sanofi, Regeneron; she is a Data Safety Monitoring Board member of GlaxoSmithKline, Sanofi, Janssen; she is an advisory board member of IASLC; outside the submitted work;

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Dr Nowak reports grants and fees from Bayer Pharmaceuticals; Roche Pharmaceuticals; Boehringer Ingelheim; Merck Sharpe Dohme; Douglas Pharmaceuticals, Atara Biotherapeutics, Astra Zeneca (payment to institution); Pharmabcine; Trizell Ltd; Seagen; honoraria from Bristol Myers Squibb and her institution received grants from AstraZeneca and Douglas Pharmaceuticals, outside the submitted work.

Contributorship statement

Conception and design of study: Nowak, Forde, Stockler, Ramalingam, Brahmer, Pavlakis, Brown, Sun, Hughes, Kok

Conduct of study: Cummins, Ford, Fitzpatrick, Bricker,

Acquisition of data: Ford, Fitzpatrick, Bricker

Drafting the manuscript: Kok, Ford, Fitzpatrick, Bricker

Revising the manuscript critically for important intellectual content: Nowak, Forde, Stockler, Brown Hughes, Pavlakis, Cook, Lesterhuis, Yip, Cummins.

Approval of the version of the manuscript to be published: Kok, Forde, Hughes, Sun, Brown, Ramalingam, Cook, Lesterhuis, Yip, O'Byrne, Pavlakis, Brahmer, Anagnostou, Ford, Fitzpatrick, Bricker, Cummins, Stockler, Nowak.

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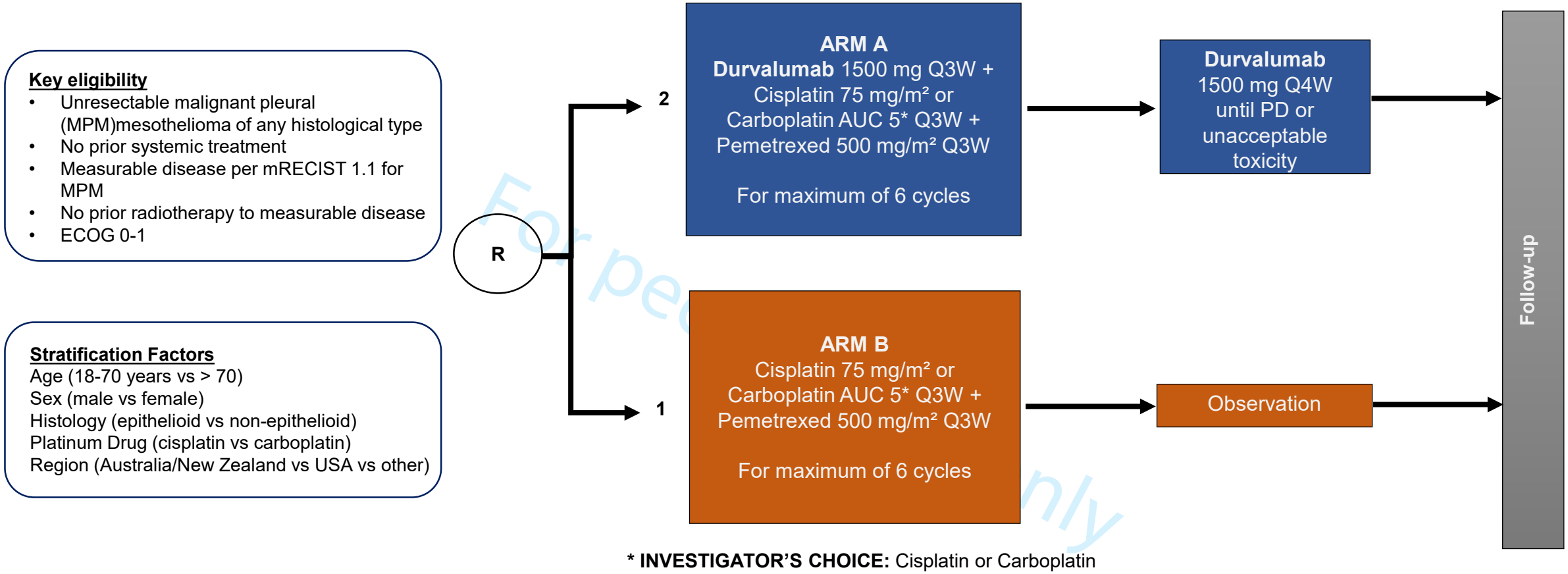

Primary endpoint: OS
Secondary endpoints: PFS, OTRR, AEs, HRQoL, healthcare resources
Tertiary endpoints: Possible prognostic/predictive biomarkers in tissue and serial blood samples: PD-L1, HLA subtypes, tumour mutation burden, genomic characteristics; validation of radiological measures of response and radiomic biomarkers

Figure 1: Study schema for DREAM3R.
Abbreviations **:** AEs, adverse events, HRQoL, health-related quality of life, HLA, human leukocyte antigen, OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival

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Protocol of DREAM3R- DuRvalumab with chEmotherapy as first line treAtment in advanced pleural Mesothelioma - A phase 3 Randomised trial

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Protocol of DREAM3R- DuRvalumab with chEmotherapy as first line treAtment in advanced pleural Mesothelioma - A phase 3 Randomised trial.

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Abstract

Introduction

There is a strong theoretical rationale for combining checkpoint blockade with cytotoxic chemotherapy in pleural mesothelioma and other cancers. Two recent single-arm, phase 2 trials (DREAM and PrE0505) combining the PD-L1 inhibitor durvalumab with standard first line chemotherapy exceeded pre-specified safety and activity criteria to proceed to a phase 3 confirmatory trial to assess this combination.

Methods and analysis

This multicentre open-label randomised trial will recruit 480 treatment-naïve adults with advanced pleural mesothelioma, randomised (2:1) to either 3-weekly durvalumab 1500mg plus 3-weekly doublet chemotherapy (cisplatin 75mg/m^2 or carboplatin AUC 5 and pemetrexed 500mg/m^2) 4-6 cycles, followed by 4-weekly durvalumab 1500mg until disease progression, unacceptable toxicity or patient withdrawal; OR doublet chemotherapy alone for 4-6 cycles, followed by observation. The target accrual time is 27 months, with follow up for an additional 24 months. This provides over 85% power if the true hazard ratio for overall survival (OS) is 0.70, with 2-sided alpha of 0.05, assuming a median OS of 15 months in the control group. Randomisation is stratified by age (18-70 years vs. > 70), sex, histology (epithelioid vs. non-epithelioid), platinum agent (cisplatin vs. carboplatin) and region (USA vs. Australia/ New Zealand vs. Other). The primary endpoint is OS. Secondary endpoints include progression-free survival, objective tumour response (by mRECIST 1.1 and iRECIST), adverse events, health-related quality of life, and healthcare resource use. Tertiary

correlative objectives are to explore and validate potential prognostic and/or predictive biomarkers (including features identified in the DREAM and PrE0505 studies, PD-L1 expression, tumour mutational burden, genomic characteristics, and HLA subtypes) in tissue and serial blood samples. An imaging databank will be assembled for validation of radiological measures of response, and studies of possible radiomic biomarkers in mesothelioma.

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Ethics and dissemination

The protocol was approved by human research ethics review committees for all participating sites. Results will be disseminated in peer-reviewed journals and at scientific conferences.

Drug Supply

AstraZeneca

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Strengths and limitations of this study

- International, open-labelled, randomised phase 3 trial of immunotherapy and chemotherapy in first line treatment of pleural mesothelioma.
- Strong biological rationale and earlier phase clinical data
- Extensive translational science biospecimen collection and plans
- This study does not contain a comparator arm of ipilimumab-nivolumab combination, which is an option for first line treatment, particularly for sarcomatoid disease
- The control arm (Cisplatin/Carboplatin plus pemetrexed) does not include bevacizumab, which is an option for first line treatment.

Introduction

The incidence of pleural mesothelioma continues to rise worldwide, particularly in Asia, despite bans on using asbestos in many countries.[1] The annual incidence rates in the UK, Australia and the USA in 2019-2021 were 6.8, 4.2 and 1.51 per 100,000 people, respectively.[2-4] Once diagnosed, mesothelioma is generally incurable and has a median survival of less than one year. Systemic treatment with palliative intent is the only option for the majority of patients.[5-7] Hundreds of thousands of people worldwide will require systemic therapy for mesothelioma in coming decades.

Current Treatment Options in Mesothelioma

Since 2003, the standard first line chemotherapy for advanced unresectable pleural mesothelioma has been platinum-based chemotherapy with 4-6 cycles of cisplatin or carboplatin, with Pemetrexed. This provides a median survival benefit of approximately 3 months over cisplatin alone in the pivotal trail, and benefits in patient-reported outcomes.[5-8] More recently, the combination of chemotherapy with bevacizumab, a vascular endothelial growth factor inhibitor, demonstrated an additional median survival benefit of 2 months.[9] However, this combination was not approved by the US FDA and most other regulatory bodies. Addition of the multi-targeted tyrosine kinase inhibitor nintedanib to chemotherapy also resulted in a progression-free survival (PFS) benefit in a randomised phase 2 trial, but a subsequent randomised phase 3 trial was negative.[10] The majority of patients who respond to first line therapy experience tumor progression soon after it is completed. Thus, there has been a strong unmet clinical need to improve first line systemic therapy in mesothelioma.

Rationale for Immunotherapy in Mesothelioma

The activity of immunotherapy in mesothelioma has been demonstrated in second and subsequent line studies.[11-18] In earlier studies, outcomes with single agent immunotherapy varied with the population and setting, but clearly indicated activity. The recent randomised phase 3 PROMISE trial showed similar outcomes with single agent pembrolizumab versus

single agent chemotherapy when used as second line treatment.[17] However, nivolumab provided benefits in progression-free and overall survival in comparison with best supportive care in the second- or subsequent-line setting. Trials of dual immunotherapy as second line treatment have shown longer PFS than single agent immunotherapy in the MAPS-2[14] and NIBIT-MESO-1[19] studies, however these observations require further validation in larger trials with OS as the primary end point to outweigh the toxicities of dual immunotherapy.

The recently reported results of the CheckMate-743 phase 3 randomised trial of dual immunotherapy with ipilimumab and nivolumab as first line chemotherapy showed a significant improvement in OS when compared with a platinum-based doublet (HR 0.74; 95% CI 0.60-0.91; p=0.002).[20] However, the OS benefit was observed predominantly in the subgroup with non-epithelioid histology (25% of participants), rather than among the more common subgroup with epithelioid histology (75% of participants). There was also no benefit observed in PFS or objective response rate (ORR) compared with chemotherapy.

First line combination of immunotherapy and chemotherapy

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1. The proposed mechanism of action for durvalumab is interference in the interaction of PD-L1 with PD1 and CD80 (B7.1). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell dependent mechanism.[21] Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response.

Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/interstitial lung disease (ILD), endocrinopathies (i.e., events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases,

nephritis/increases in creatinine, rash/dermatitis including pemphigoid, myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (e.g., Guillain-Barré syndrome, myasthenia gravis).

Two recent single-arm first line phase 2 trials[22,23] combining durvalumab with platinum-based doublet chemotherapy showed encouraging activity and acceptable safety in advanced mesothelioma of all subtypes. The Australian DREAM trial of 54 participants exceeded its pre-specified target with a 6-month PFS rate of 57%.[22] The ORR was 48%, median PFS was 7 months by mRECIST and iRECIST; median OS was 18 months In the US-based PrECOG 0505 trial of 55 participants, the median OS was 20.4 months, 12-month OS rate was 70% (95% CI 56-81), ORR was 56%, 6-month PFS rate was 69.1% and median PFS was 7 months.[23]

DREAM3R was designed and developed before results from CheckMate-743 were available. The positive results of CheckMate-743 strengthen the strong rationale for DREAM3R. The OS benefit in Checkmate-743 was uncertain in the subgroup with epithelioid histology, and not evident in the subgroup with tumours that did not express PD-L1. Results of translational research studies to identify those more likely to benefit are pending.

Given the favourable OS and PFS data from the DREAM and PrE0505 trials, DREAM3R aims to determine the effectiveness of adding durvalumab to cisplatin/carboplatin and pemetrexed. Our primary hypothesis is that the addition of durvalumab will prolong OS in comparison with platinum and pemetrexed alone.

Methods and analyses

Trial design

The DREAM3R trial is an international, open label, randomised (2:1), multi-centre, phase 3 trial. The planned study sites include 29 in Australia, 1 in New Zealand and 30 from the USA.

Participants are randomised in a ratio of 2:1 to either durvalumab + chemotherapy or chemotherapy alone, by a central computerized system that uses permuted blocks to stratify for (see Figure 1):

1. Age (18-70 years vs older than 70)
2. Sex (male vs female)
3. Histology (epithelioid vs non-epithelioid)
4. Region (Australia/New Zealand vs USA vs other)
5. Platinum agent (cisplatin vs carboplatin)

Inclusion criteria

Participants who fulfil these criteria are considered eligible:

- Adults with a histological diagnosis of pleural mesothelioma of any histological type, that is not amenable to curative surgical resection. Histological diagnosis requires tumour tissue from an open biopsy, or a core biopsy with a needle of 19 gauge or wider.
- Measurable disease per mRECIST 1.1 for pleural mesothelioma
- No prior radiotherapy to measurable disease
- Eastern Cooperative Oncology Group (ECOG) score 0 to 1
- Tumour tissue (FFPE) available from diagnostic biopsy for PD-L1
- Adequate blood tests (done within 14 days prior to randomisation) and with values within the ranges specified below. Blood transfusions are permissible if completed at least 7 days prior to treatment start.
    - Haemoglobin ≥ 9.0 g/L
    - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    - Platelets $\geq 100 \times 10^9$/L

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (except participants with Gilbert's Syndrome, who are eligible with bilirubin ≤ 2.5 ULN)
- Alanine transaminase ≤ 2.5 x upper limit of normal (ULN), unless liver metastases or invasion are present, in which case it must be ≤ 5 x ULN
- Aspartate aminotransferase ≤ 2.5 x ULN, unless liver metastases or invasion are present, in which case it must be ≤ 5 x ULN
- Creatinine clearance (CrCl) ≥ 45 mL/min (per Cockcroft-Gault formula)

- Life expectancy at least 12 weeks
- Women of childbearing potential must use a reliable means of contraception during treatment and for at least 90 days thereafter. Breastfeeding is not permissible during or for at least 90 days after the final study treatment. Men must have been surgically sterilised or use a (double if required) barrier method of contraception if they are sexually active with a woman of child bearing potential
- Evidence of post-menopausal status or negative serum pregnancy test for female pre-menopausal participants. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause.

Exclusion criteria

Participants who meet the following criteria are considered ineligible

- Received prior chemotherapy, immune checkpoint inhibitor or other systemic anti-cancer therapy for pleural mesothelioma
- Diagnosis on cytology or fine needle aspiration only
- Contraindication for immune checkpoint inhibitor such as active or documented autoimmune or inflammatory disorder

- Any condition requiring systemic treatment with corticosteroids (>10mg daily prednisone or equivalent) or other immunosuppressive medications within 28 days
- Symptomatic or uncontrolled brain or leptomeningeal metastases
- Hearing loss or peripheral neuropathy considered by the investigators to contraindicate cisplatin administration
- History of allergy or hypersensitivity to investigational product, cisplatin, pemetrexed or any excipient.
- No other malignancy that requires active treatment. Participants with a past history of adequately treated carcinoma in situ, non-melanoma skin cancer or lentigo maligna without evidence of disease or superficial transitional cell carcinoma of the bladder are eligible.
- Current treatment or treatment within the last 12 months with any investigational anti-cancer products.
- Concurrent enrolment in another clinical trial testing an anticancer treatment.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive cardiac failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, active peptic ulcer disease or gastritis, serious chronic gastrointestinal conditions associated with diarrhoea, active bleeding diatheses.
- Hepatitis B, hepatitis C or human immunodeficiency virus (HIV). Exceptions include past or resolved Hepatitis B (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) and participants positive for hepatitis C (HCV) antibody if polymerase chain reaction is negative for HCV RNA. HIV testing is not required in absence of clinical suspicion of HIV.

- Known history of primary immunodeficiency, allogeneic organ transplant, pneumonitis or active tuberculosis.
- Receipt of live attenuated vaccination within 30 days prior to enrolment or within 30 days of receiving durvalumab.

Study objectives

The primary objective of DREAM3R trial is to determine the effects of adding durvalumab on OS. Secondary objectives are to determine effects on

PFS (by mRECIST 1.1 for pleural mesothelioma and iRECIST)

Objective tumour response [(OTR) by mRECIST 1.1 for pleural mesothelioma and iRECIST]

Adverse events according to Common Terminology Criteria (CTCAE v5.0)

Health-related quality of life (HRQL, EORTC QLQ-C30, QLQ LC-29, EQ-5D-5L)

Healthcare resource use

Incremental cost-effectiveness

Tertiary/ correlative objectives are

To explore and validate potential prognostic or predictive biomarkers of clinical outcomes, (including but not limited to candidates identified in the phase II DREAM and PrE0505 studies, PD-L1 expression, HLA type, T cell tumour infiltration, T cell receptor repertoire, tumour mutational burden and gene signatures)

To collect an imaging databank for future validation of radiological response metrics in pleural mesothelioma

Treatment arms

Investigational arm (Arm A)

Standard doublet chemotherapy + durvalumab, followed by durvalumab maintenance (see Table 1)

Cisplatin/ carboplatin and pemetrexed are administered before durvalumab. Durvalumab is administered immediately following or during the final hydration IV fluid bag for cisplatin/ carboplatin administration.

Chemotherapy is continued for a maximum of 6 cycles in the absence of prohibitibve toxicity (e.g. cumulative neuropathy, hearing impairment, kidney impairment). However, after the patient has completed 4 cycles it is up to the judgement of the site investigator whether to complete all 6 cycles.

Durvalumab is continued if chemotherapy is stopped prior to completion of 6 cycles in participants with tumors that are stable or responding to treatment.

For participants entering into the maintenance stage, the first dose of durvalumab should commence 3 weeks after the last dose of chemo-durvalumab. Subsequent treatments with durvalumab will continue at 1500 mg on Day 1 of a **4-weekly cycle** in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or other reasons for discontinuation.

Control arm (Arm B)

Standard doublet chemotherapy followed by close observation (see Table 2).

In both arms

Carboplatin AUC 5 is the initial platinum agent of choice in participants with an estimated creatinine clearance 45 to 59 mL/min, or those with clinically reported hearing loss.

Carboplatin or cisplatin may be chosen for other participants at the discretion of investigators.

Participants experiencing unacceptable cisplatin toxicities may be treated subsequently with carboplatin AUC 5 every 3 weeks. Regimens for antiemetic and hydration are as per local institutional guidelines.

Trial oversight and monitoring

DREAM3R is an investigator-initiated, academic trial, conducted as a collaboration between the Thoracic Oncology Group of Australasia (TOGA), the NHMRC Clinical Trials Centre at the University of Sydney, and PrECOG, a non-profit research company that focuses on cancer clinical trials. The University of Sydney is the sponsor in Australia and New Zealand, PrECOG is the sponsor in USA. This international study will be conducted through a number of regional coordinating centres, each responsible for their own ethics and regulatory approvals, regional monitoring, medical oversight and facilitation of data collection and query resolution. The NHMRC Clinical Trials Centre will be responsible for study coordination, data acquisition, management, and statistical analysis.

The trial will be monitored by an Independent Safety and Data Monitoring Committee (ISDMC) approximately every 6 months. The ISDMC will advise the Trial Monitoring Committee (TMC) regarding safety, specified matters related to the integrity and potential conclusions of trial data, and the appropriateness of continued trial conduct.

The International Trial Steering Committee (ITSC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). The ITSC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on safety monitoring or other information.

Each regional coordinating centre will constitute its own regional TMC, including a clinical lead and coordinating centre lead who will represent the region on the ITSC.

Changes and amendments to the protocol can only be initiated and made by the ITSC. Approval of protocol amendments by the Institutional Human Research Ethics Committees is required prior to their implementation.

Patient and Public Involvement

Patient and members of the public were involved at several stages of the trial, including the design, management, and conduct of the trial. We received input from mesothelioma patients in the design of the trial materials and management oversight through membership of the trial steering committee. We carefully assessed the burden of the trial interventions on patients. We intend to disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

Statistical considerations

Sample size

Enrolment of 480 participants (randomised 2:1) over 27 months and followed for at least another 24 months, provides >85% power assuming a true hazard ratio of 0.70, a median survival of 15 months in the control group and a median survival of 21.4 months in the durvalumab group. The alternate hypothesis (difference) will be tested against the null hypothesis (no difference) with a 2-sided alpha of 0.05. There is an allowance for non-compliance with assigned treatment of 6%.

A single interim analysis will be conducted according to the alpha spending approach using an O'Brien-Fleming boundary. The interim analysis will be conducted at least 6 months after the completion of recruitment and having observed 50% events required for the final analysis. The exact boundary will be computed prior to the analysis according to the percentage of information observed. For example, at exactly 50% information (176 events) the analysis would use alpha=0.0031 and declare a significant result if the observed HR<0.64. The final analysis (352 events) would then be based on with alpha 0.049 and have power of 85% if the true HR was 0.70.

Statistical analysis

All randomised participants will be included in the analysis. With the exception of safety data, all analyses will be conducted on an intention to treat basis (safety analysis will be

reported by treatment as received within all participants who received any study treatment). 95% confidence intervals (CI) will be reported for all relevant estimates. A statistical analysis plan will be prepared prior to the final analysis. This document will contain additional detail on the methods described here.

The primary endpoint of the study is OS, defined as the time from randomisation to the date of death due to any cause. Participants who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last known alive date. All randomised participants will be included in the analysis of OS. Kaplan-Meier estimates will be computed for both groups. CI for the median survival will be computed by the method of Brookmeyer and Crowley. In the primary analysis, the two treatment arms will be compared using the log-rank test stratified by stratification factors. Cox regression modelling will be used to estimate the treatment effect both on an unadjusted basis and adjusted for stratification variables.

PFS is a secondary endpoint of this study, defined as the time from randomisation to the date of the first documented disease progression (based on mRECIST and iRECIST) or death due to any cause. A patient who stops treatment with study drug and goes on to receive alternative therapy for pleural mesothelioma, prior to documentation of disease progression, will be censored on the date alternative therapy began. If a patient has not progressed or received alternative therapy, PFS will be censored on the date of the last disease assessment. All randomised participants will be included in the analysis of PFS. All analyses for OS will be similarly performed for PFS.

OTR rate is defined as the proportion of participants with a documented complete response, partial response (CR + PR) based on iRECIST criteria. Results for tumor-related endpoints (PFS and ORR) based on iRECIST will be considered exploratory. The primary estimate of OTRR will be based on all participants randomised, and compared using Cochran-Mantel-

Haenszel test stratified by stratification factors. Quality of life analysis will be conducted with appropriate methods to account for repeated measures.

An exploratory analysis of biomarkers (from tissue, serial bloods) and their associations with clinical endpoints will be conducted. These exploratory analyses will be descriptive/graphical in nature, and are designed to generate new hypotheses to be tested in future clinical studies. Where parameters of immune response are measured, continuous variables will be summarized with means and standard deviations. Dichotomous and categorical variables will be summarized using proportions with exact 95% confidence intervals and counts, respectively. These summaries will be computed for each treated patient at multiple time points, before and after treatment administration, as indicated in the study schema. Plots will be used to show the changes in immune response over time for each individual. For each patient, comparisons in the pre- and post-durvalumab responses will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and McNemars test for dichotomous or categorical variables. Associations between immune responses will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g. correlations, $\chi 2$ tests).

Ethics and Dissemination

The study will be conducted according to the ICH Guideline for Good Clinical Practice Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6(R2) dated 9 November 2016, the principles laid down by the World Medical Association in the Declaration of Helsinki 2013 and pertinent regional regulations.

The study gained central ethical approval for Australia and New Zealand sites from the Sydney Local Health District Ethics Review Committee (RPAH Zone) (2019/ETH13618) on 17 February 2021 and Northern B Health and Disability Ethics Committee on 26th January

2021. USA sites received initial approval December 28, 2020 from WCG IRB Puyallup, Washington.

Trial status

Patient enrolment commenced in February 2021 at Sir Charles Gardiner Hospital, Perth, Australia. As of the 15th September 2021, 41 of the 60 planned sites have opened to recruitment and 45 participants have been randomised.

Word count: 3192 (max 3500)

Figure

Figure 1: Schema for DREAM3R

Tables

Table 1: Investigational arm treatment

Agent (s)	Dose	Route	Duration	Schedule	Frequency
Cisplatin OR Carboplatin	75 mg/m^2 OR AUC 5	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Pemetrexed	500 mg/m^2	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Durvalumab	1500 mg	IV	60 minutes	Day 1 each cycle	Every 3 weeks
Followed by Maintenance					
Durvalumab	1500 mg	IV	60 minutes	Day 1 each cycle	**Every 4 weeks** Until disease progression/ unacceptable toxicity/ withdrawal of consent

Table 2: Control arm treatment

Agent (s)	Dose	Route	Duration	Schedule	Frequency
Cisplatin OR Carboplatin	75 mg/m^2 OR AUC 5	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Pemetrexed	500 mg/m^2	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Followed by					
Close observation per standard of care					

Conflict of interest

Dr Sun, Dr Brown, Dr Cook, Dr Yip, Ms Ford, Ms Fitzpatrick, Ms Bricker, Ms Cummins have nothing to disclose.

Dr Kok reports grants and fees from AstraZeneca and Pfizer, she is a consultant/ advisory board member of MSD, outside the submitted work;

Dr. Forde reports grants and fees from AstraZeneca, BMS, Corvus, Novartis, Kyowa; he is a consultant/ advisory board member of Amgen, AstraZeneca, BMS, Novartis, Janssen, Iteos, Mirati, Sanofi; he is a Data Safety Monitoring Board member of Polaris, Flame, outside the submitted work;

Dr Hughes is a consultant/ advisory board member of MSD, BMS, Roche, Pfizer, AstraZeneca, Eisai, Takeda; his institution received grants from Amgen, outside the submitted work;

Dr Ramalingam reports grants and fees from Amgen, AstraZeneca, Genmab, Eisai, Lilly, Roche, Merck, Takeda and GSK; he is a Data Safety Monitoring Board member of Jansen; a member of Board for Gergia Society of Oncology and IASLC; his institution received grants from AstraZenca, Amgen, BMS, Merck, Genmab, Takeda, Advaxis and Pfizer, outside the submitted work;

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Contributorship statement

Conception and design of study: Nowak, Forde, Stockler, Ramalingam, Brahmer, Pavlakis, Brown, Sun, Hughes, Kok

Conduct of study: Cummins, Ford, Fitzpatrick, Bricker,

Acquisition of data: Ford, Fitzpatrick, Bricker

Drafting the manuscript: Kok, Ford, Fitzpatrick, Bricker

Revising the manuscript critically for important intellectual content: Nowak, Forde, Stockler, Brown Hughes, Pavlakis, Cook, Lesterhuis, Yip, Cummins.

Approval of the version of the manuscript to be published: Kok, Forde, Hughes, Sun, Brown, Ramalingam, Cook, Lesterhuis, Yip, O'Byrne, Pavlakis, Brahmer, Anagnostou, Ford, Fitzpatrick, Bricker, Cummins, Stockler, Nowak.

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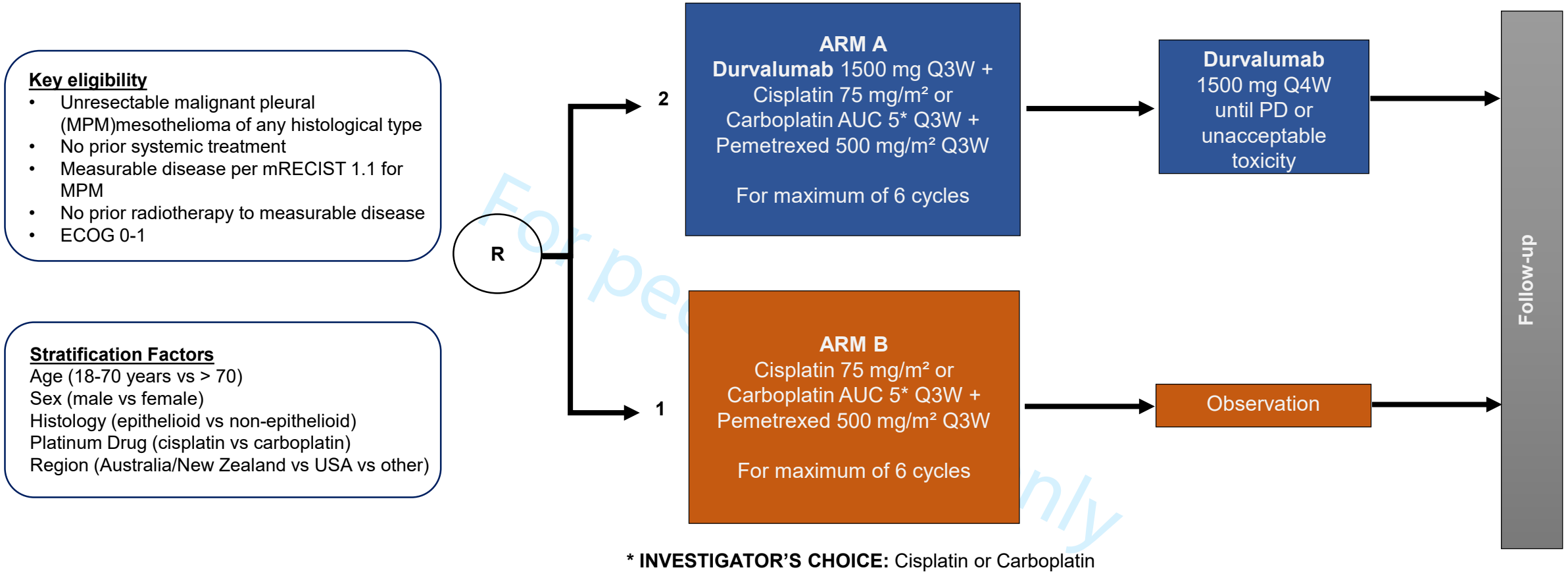

Primary endpoint: OS
Secondary endpoints: PFS, OTRR, AEs, HRQoL, healthcare resources
Tertiary endpoints: Possible prognostic/predictive biomarkers in tissue and serial blood samples: PD-L1, HLA subtypes, tumour mutation burden, genomic characteristics; validation of radiological measures of response and radiomic biomarkers

Figure 1: Study schema for DREAM3R.
Abbreviations **:** AEs, adverse events, HRQoL, health-related quality of life, HLA, human leukocyte antigen, OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival

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Protocol of DREAM3R- DuRvalumab with chEmotherapy as first line treAtment in advanced pleural Mesothelioma - A phase 3 Randomised trial

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Protocol of DREAM3R- DuRvalumab with chEmotherapy as first line treAtment in advanced pleural Mesothelioma - A phase 3 Randomised trial.

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Abstract

Introduction

There is a strong theoretical rationale for combining checkpoint blockade with cytotoxic chemotherapy in pleural mesothelioma and other cancers. Two recent single-arm, phase 2 trials (DREAM and PrE0505) combining the PD-L1 inhibitor durvalumab with standard first line chemotherapy exceeded pre-specified safety and activity criteria to proceed to a phase 3 confirmatory trial to assess this combination.

Methods and analysis

This multicentre open-label randomised trial will recruit 480 treatment-naïve adults with advanced pleural mesothelioma, randomised (2:1) to either 3-weekly durvalumab 1500mg plus 3-weekly doublet chemotherapy (cisplatin 75mg/m^2 or carboplatin AUC 5 and pemetrexed 500mg/m^2) 4-6 cycles, followed by 4-weekly durvalumab 1500mg until disease progression, unacceptable toxicity or patient withdrawal; OR doublet chemotherapy alone for 4-6 cycles, followed by observation. The target accrual time is 27 months, with follow up for an additional 24 months. This provides over 85% power if the true hazard ratio for overall survival (OS) is 0.70, with 2-sided alpha of 0.05, assuming a median OS of 15 months in the control group. Randomisation is stratified by age (18-70 years vs. > 70), sex, histology (epithelioid vs. non-epithelioid), platinum agent (cisplatin vs. carboplatin) and region (USA vs. Australia/ New Zealand vs. Other). The primary endpoint is OS. Secondary endpoints include progression-free survival, objective tumour response (by mRECIST 1.1 and iRECIST), adverse events, health-related quality of life, and healthcare resource use. Tertiary

correlative objectives are to explore and validate potential prognostic and/or predictive biomarkers (including features identified in the DREAM and PrE0505 studies, PD-L1 expression, tumour mutational burden, genomic characteristics, and HLA subtypes) in tissue and serial blood samples. An imaging databank will be assembled for validation of radiological measures of response, and studies of possible radiomic biomarkers in mesothelioma.

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Ethics and dissemination

The protocol was approved by human research ethics review committees for all participating sites. Results will be disseminated in peer-reviewed journals and at scientific conferences.

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Strengths and limitations of this study

- International, open-labelled, randomised phase 3 trial of immunotherapy and chemotherapy in first line treatment of pleural mesothelioma.
- Strong biological rationale and earlier phase clinical data
- Extensive translational science biospecimen collection and plans
- This study does not contain a comparator arm of ipilimumab-nivolumab combination, which is an option for first line treatment, particularly for sarcomatoid disease
- The control arm (Cisplatin/Carboplatin plus pemetrexed) does not include bevacizumab, which is an option for first line treatment.

Introduction

The incidence of pleural mesothelioma continues to rise worldwide, particularly in Asia, despite bans on using asbestos in many countries.[1] The annual incidence rates in the UK, Australia and the USA in 2019-2021 were 6.8, 4.2 and 1.51 per 100,000 people, respectively.[2-4] Once diagnosed, mesothelioma is generally incurable and has a median survival of less than one year. Systemic treatment with palliative intent is the only option for the majority of patients.[5-7] Hundreds of thousands of people worldwide will require systemic therapy for mesothelioma in coming decades.

Current Treatment Options in Mesothelioma

Since 2003, the standard first line chemotherapy for advanced unresectable pleural mesothelioma has been platinum-based chemotherapy with 4-6 cycles of cisplatin or carboplatin, with Pemetrexed. This provides a median survival benefit of approximately 3 months over cisplatin alone in the pivotal trail, and benefits in patient-reported outcomes.[5-8] More recently, the combination of chemotherapy with bevacizumab, a vascular endothelial growth factor inhibitor, demonstrated an additional median survival benefit of 2 months.[9] However, this combination was not approved by the US FDA and most other regulatory bodies. Addition of the multi-targeted tyrosine kinase inhibitor nintedanib to chemotherapy also resulted in a progression-free survival (PFS) benefit in a randomised phase 2 trial, but a subsequent randomised phase 3 trial was negative.[10] The majority of patients who respond to first line therapy experience tumor progression soon after it is completed. Thus, there has been a strong unmet clinical need to improve first line systemic therapy in mesothelioma.

Rationale for Immunotherapy in Mesothelioma

The activity of immunotherapy in mesothelioma has been demonstrated in second and subsequent line studies.[11-18] In earlier studies, outcomes with single agent immunotherapy varied with the population and setting, but clearly indicated activity. The recent randomised phase 3 PROMISE trial showed similar outcomes with single agent pembrolizumab versus

single agent chemotherapy when used as second line treatment.[17] However, nivolumab provided benefits in progression-free and overall survival in comparison with best supportive care in the second- or subsequent-line setting. Trials of dual immunotherapy as second line treatment have shown longer PFS than single agent immunotherapy in the MAPS-2[14] and NIBIT-MESO-1[19] studies, however these observations require further validation in larger trials with OS as the primary end point to outweigh the toxicities of dual immunotherapy.

The recently reported results of the CheckMate-743 phase 3 randomised trial of dual immunotherapy with ipilimumab and nivolumab as first line chemotherapy showed a significant improvement in OS when compared with a platinum-based doublet (HR 0.74; 95% CI 0.60-0.91; p=0.002).[20] However, the OS benefit was observed predominantly in the subgroup with non-epithelioid histology (25% of participants), rather than among the more common subgroup with epithelioid histology (75% of participants). There was also no benefit observed in PFS or objective response rate (ORR) compared with chemotherapy.

First line combination of immunotherapy and chemotherapy

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1. The proposed mechanism of action for durvalumab is interference in the interaction of PD-L1 with PD1 and CD80 (B7.1). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell dependent mechanism.[21] Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response.

Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/interstitial lung disease (ILD), endocrinopathies (i.e., events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases,

nephritis/increases in creatinine, rash/dermatitis including pemphigoid, myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (e.g., Guillain-Barré syndrome, myasthenia gravis).

Two recent single-arm first line phase 2 trials[22,23] combining durvalumab with platinum-based doublet chemotherapy showed encouraging activity and acceptable safety in advanced mesothelioma of all subtypes. The Australian DREAM trial of 54 participants exceeded its pre-specified target with a 6-month PFS rate of 57%.[22] The ORR was 48%, median PFS was 7 months by mRECIST and iRECIST; median OS was 18 months In the US-based PrECOG 0505 trial of 55 participants, the median OS was 20.4 months, 12-month OS rate was 70% (95% CI 56-81), ORR was 56%, 6-month PFS rate was 69.1% and median PFS was 7 months.[23]

DREAM3R was designed and developed before results from CheckMate-743 were available. The positive results of CheckMate-743 strengthen the strong rationale for DREAM3R. The OS benefit in Checkmate-743 was uncertain in the subgroup with epithelioid histology, and not evident in the subgroup with tumours that did not express PD-L1. Results of translational research studies to identify those more likely to benefit are pending.

Given the favourable OS and PFS data from the DREAM and PrE0505 trials, DREAM3R aims to determine the effectiveness of adding durvalumab to cisplatin/carboplatin and pemetrexed. Our primary hypothesis is that the addition of durvalumab will prolong OS in comparison with platinum and pemetrexed alone.

Methods and analyses

Trial design

The DREAM3R trial is an international, open label, randomised (2:1), multi-centre, phase 3 trial. The planned study sites include 29 in Australia, 1 in New Zealand and 30 from the USA.

Participants are randomised in a ratio of 2:1 to either durvalumab + chemotherapy or chemotherapy alone, by a central computerized system that uses permuted blocks to stratify for (see Figure 1):

1. Age (18-70 years vs older than 70)
2. Sex (male vs female)
3. Histology (epithelioid vs non-epithelioid)
4. Region (Australia/New Zealand vs USA vs other)
5. Platinum agent (cisplatin vs carboplatin)

ECOG is not a stratification factor. It is unlikely that that there will be equal numbers of ECOG 0 and ECOG 1 recruited.

Inclusion criteria

Participants who fulfil these criteria are considered eligible:

- Adults with a histological diagnosis of pleural mesothelioma of any histological type, that is not amenable to curative surgical resection. Histological diagnosis requires tumour tissue from an open biopsy, or a core biopsy with a needle of 19 gauge or wider.
- Measurable disease per mRECIST 1.1 for pleural mesothelioma
- No prior radiotherapy to measurable disease
- Eastern Cooperative Oncology Group (ECOG) score 0 to 1
- Tumour tissue (FFPE) available from diagnostic biopsy for PD-L1
- Adequate blood tests (done within 14 days prior to randomisation) and with values within the ranges specified below. Blood transfusions are permissible if completed at least 7 days prior to treatment start.
    - Haemoglobin ≥ 9.0 g/L

- Absolute neutrophil count ≥ 1.5 x 10^9/L
- Platelets ≥ 100 x 10^9/L
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) (except participants with Gilbert's Syndrome, who are eligible with bilirubin ≤ 2.5 ULN)
- Alanine transaminase ≤ 2.5 x upper limit of normal (ULN), unless liver metastases or invasion are present, in which case it must be ≤ 5 x ULN
- Aspartate aminotransferase ≤ 2.5 x ULN, unless liver metastases or invasion are present, in which case it must be ≤ 5 x ULN
- Creatinine clearance (CrCl) ≥ 45 mL/min (per Cockcroft-Gault formula)

- Life expectancy at least 12 weeks
- Women of childbearing potential must use a reliable means of contraception during treatment and for at least 90 days thereafter. Breastfeeding is not permissible during or for at least 90 days after the final study treatment. Men must have been surgically sterilised or use a (double if required) barrier method of contraception if they are sexually active with a woman of child bearing potential
- Evidence of post-menopausal status or negative serum pregnancy test for female pre-menopausal participants. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause.

Exclusion criteria

Participants who meet the following criteria are considered ineligible

- Received prior chemotherapy, immune checkpoint inhibitor or other systemic anti-cancer therapy for pleural mesothelioma
- Diagnosis on cytology or fine needle aspiration only

- Contraindication for immune checkpoint inhibitor such as active or documented autoimmune or inflammatory disorder
- Any condition requiring systemic treatment with corticosteroids (>10mg daily prednisone or equivalent) or other immunosuppressive medications within 28 days
- Symptomatic or uncontrolled brain or leptomeningeal metastases
- Hearing loss or peripheral neuropathy considered by the investigators to contraindicate cisplatin administration
- History of allergy or hypersensitivity to investigational product, cisplatin, pemetrexed or any excipient.
- No other malignancy that requires active treatment. Participants with a past history of adequately treated carcinoma in situ, non-melanoma skin cancer or lentigo maligna without evidence of disease or superficial transitional cell carcinoma of the bladder are eligible.
- Current treatment or treatment within the last 12 months with any investigational anti-cancer products.
- Concurrent enrolment in another clinical trial testing an anticancer treatment.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive cardiac failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, active peptic ulcer disease or gastritis, serious chronic gastrointestinal conditions associated with diarrhoea, active bleeding diatheses.
- Hepatitis B, hepatitis C or human immunodeficiency virus (HIV). Exceptions include past or resolved Hepatitis B (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) and participants positive for hepatitis C (HCV)

antibody if polymerase chain reaction is negative for HCV RNA. HIV testing is not required in absence of clinical suspicion of HIV.

- Known history of primary immunodeficiency, allogeneic organ transplant, pneumonitis or active tuberculosis.
- Receipt of live attenuated vaccination within 30 days prior to enrolment or within 30 days of receiving durvalumab.

Study objectives

The primary objective of DREAM3R trial is to determine the effects of adding durvalumab on OS. Secondary objectives are to determine effects on

PFS (by mRECIST 1.1 for pleural mesothelioma and iRECIST)

Objective tumour response [(OTR) by mRECIST 1.1 for pleural mesothelioma and iRECIST]

Adverse events according to Common Terminology Criteria (CTCAE v5.0)

Health-related quality of life (HRQL, EORTC QLQ-C30, QLQ LC-29, EQ-5D-5L)

Healthcare resource use

Incremental cost-effectiveness

Tertiary/ correlative objectives are

To explore and validate potential prognostic or predictive biomarkers of clinical outcomes, (including but not limited to candidates identified in the phase II DREAM and PrE0505 studies, PD-L1 expression, HLA type, T cell tumour infiltration, T cell receptor repertoire, tumour mutational burden and gene signatures)

To collect an imaging databank for future validation of radiological response metrics in pleural mesothelioma

Treatment arms

Investigational arm (Arm A)

Standard doublet chemotherapy + durvalumab, followed by durvalumab maintenance (see Table 1)

Cisplatin/ carboplatin and pemetrexed are administered before durvalumab. Durvalumab is administered immediately following or during the final hydration IV fluid bag for cisplatin/ carboplatin administration.

Chemotherapy is continued for a maximum of 6 cycles in the absence of prohibitibve toxicity (e.g. cumulative neuropathy, hearing impairment, kidney impairment). However, after the patient has completed 4 cycles it is up to the judgement of the site investigator whether to complete all 6 cycles.

Durvalumab is continued if chemotherapy is stopped prior to completion of 6 cycles in participants with tumors that are stable or responding to treatment.

For participants entering into the maintenance stage, the first dose of durvalumab should commence 3 weeks after the last dose of chemo-durvalumab. Subsequent treatments with durvalumab will continue at 1500 mg on Day 1 of a **4-weekly cycle** in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or other reasons for discontinuation.

Control arm (Arm B)

Standard doublet chemotherapy followed by close observation (see Table 2).

In both arms

Carboplatin AUC 5 is the initial platinum agent of choice in participants with an estimated creatinine clearance 45 to 59 mL/min, or those with clinically reported hearing loss.

Carboplatin or cisplatin may be chosen for other participants at the discretion of investigators.

Participants experiencing unacceptable cisplatin toxicities may be treated subsequently with

carboplatin AUC 5 every 3 weeks. Regimens for antiemetic and hydration are as per local institutional guidelines.

Trial oversight and monitoring

DREAM3R is an investigator-initiated, academic trial, conducted as a collaboration between the Thoracic Oncology Group of Australasia (TOGA), the NHMRC Clinical Trials Centre at the University of Sydney, and PrECOG, a non-profit research company that focuses on cancer clinical trials. The University of Sydney is the sponsor in Australia and New Zealand, PrECOG is the sponsor in USA. This international study will be conducted through a number of regional coordinating centres, each responsible for their own ethics and regulatory approvals, regional monitoring, medical oversight and facilitation of data collection and query resolution. The NHMRC Clinical Trials Centre will be responsible for study coordination, data acquisition, management, and statistical analysis. All patients will be given written informed consent prior to study enrolment.

The trial will be monitored by an Independent Safety and Data Monitoring Committee (ISDMC) approximately every 6 months. The ISDMC will advise the Trial Monitoring Committee (TMC) regarding safety, specified matters related to the integrity and potential conclusions of trial data, and the appropriateness of continued trial conduct.

The International Trial Steering Committee (ITSC) will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). The ITSC will consider recommendations from the ISDMC about whether to continue the study as planned, modify, or stop it, based on safety monitoring or other information.

Each regional coordinating centre will constitute its own regional TMC, including a clinical lead and coordinating centre lead who will represent the region on the ITSC.

Changes and amendments to the protocol can only be initiated and made by the ITSC. Approval of protocol amendments by the Institutional Human Research Ethics Committees is required prior to their implementation.

Patient and Public Involvement

Patient and members of the public were involved at several stages of the trial, including the design, management, and conduct of the trial. We received input from mesothelioma patients in the design of the trial materials and management oversight through membership of the trial steering committee. We carefully assessed the burden of the trial interventions on patients. We intend to disseminate the main results to trial participants and will seek patient and public involvement in the development of an appropriate method of dissemination.

Statistical considerations

Sample size

Enrolment of 480 participants (randomised 2:1) over 27 months and followed for at least another 24 months, provides >85% power assuming a true hazard ratio of 0.70, a median survival of 15 months in the control group and a median survival of 21.4 months in the durvalumab group. The alternate hypothesis (difference) will be tested against the null hypothesis (no difference) with a 2-sided alpha of 0.05. There is an allowance for non-compliance with assigned treatment of 6%.

A single interim analysis will be conducted according to the alpha spending approach using an O'Brien-Fleming boundary. The interim analysis will be conducted at least 6 months after the completion of recruitment and having observed 50% events required for the final analysis. The exact boundary will be computed prior to the analysis according to the percentage of information observed. For example, at exactly 50% information (176 events) the analysis would use alpha=0.0031 and declare a significant result if the observed HR<0.64. The final

analysis (352 events) would then be based on with alpha 0.049 and have power of 85% if the true HR was 0.70.

Statistical analysis

All randomised participants will be included in the analysis. With the exception of safety data, all analyses will be conducted on an intention to treat basis (safety analysis will be reported by treatment as received within all participants who received any study treatment). 95% confidence intervals (CI) will be reported for all relevant estimates. A statistical analysis plan will be prepared prior to the final analysis. This document will contain additional detail on the methods described here.

The primary endpoint of the study is OS, defined as the time from randomisation to the date of death due to any cause. Participants who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last known alive date. All randomised participants will be included in the analysis of OS. Kaplan-Meier estimates will be computed for both groups. CI for the median survival will be computed by the method of Brookmeyer and Crowley. In the primary analysis, the two treatment arms will be compared using the log-rank test stratified by stratification factors. Cox regression modelling will be used to estimate the treatment effect both on an unadjusted basis and adjusted for stratification variables.

PFS is a secondary endpoint of this study, defined as the time from randomisation to the date of the first documented disease progression (based on mRECIST and iRECIST) or death due to any cause. A patient who stops treatment with study drug and goes on to receive alternative therapy for pleural mesothelioma, prior to documentation of disease progression, will be censored on the date alternative therapy began. If a patient has not progressed or received alternative therapy, PFS will be censored on the date of the last disease assessment. All randomised participants will be included in the analysis of PFS. All analyses for OS will be similarly performed for PFS.

OTR rate is defined as the proportion of participants with a documented complete response, partial response (CR + PR) based on iRECIST criteria. Results for tumor-related endpoints (PFS and ORR) based on iRECIST will be considered exploratory. The primary estimate of OTRR will be based on all participants randomised, and compared using Cochran-Mantel-Haenszel test stratified by stratification factors. Quality of life analysis will be conducted with appropriate methods to account for repeated measures.

An exploratory analysis of biomarkers (from tissue, serial bloods) and their associations with clinical endpoints will be conducted. These exploratory analyses will be descriptive/graphical in nature, and are designed to generate new hypotheses to be tested in future clinical studies. Where parameters of immune response are measured, continuous variables will be summarized with means and standard deviations. Dichotomous and categorical variables will be summarized using proportions with exact 95% confidence intervals and counts, respectively. These summaries will be computed for each treated patient at multiple time points, before and after treatment administration, as indicated in the study schema. Plots will be used to show the changes in immune response over time for each individual. For each patient, comparisons in the pre- and post-durvalumab responses will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and McNemars test for dichotomous or categorical variables. Associations between immune responses will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g. correlations, $\chi 2$ tests).

Ethics and Dissemination

The study will be conducted according to the ICH Guideline for Good Clinical Practice Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6(R2) dated 9 November 2016, the principles laid down by the World Medical Association in the Declaration of Helsinki 2013 and pertinent regional regulations.

The study gained central ethical approval for Australia and New Zealand sites from the Sydney Local Health District Ethics Review Committee (RPAH Zone) (2019/ETH13618) on 17 February 2021 and Northern B Health and Disability Ethics Committee on 26th January 2021. USA sites received initial approval December 28, 2020 from WCG IRB Puyallup, Washington.

Trial status

Patient enrolment commenced in February 2021 at Sir Charles Gardiner Hospital, Perth, Australia. As of the 15th September 2021, 41 of the 60 planned sites have opened to recruitment and 45 participants have been randomised.

Word count: 3192 (max 3500)

Figure

Figure 1: Schema for DREAM3R

Tables

Table 1: Investigational arm treatment

Agent (s)	Dose	Route	Duration	Schedule	Frequency
Cisplatin OR Carboplatin	75 mg/m^2 OR AUC 5	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Pemetrexed	500 mg/m^2	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Durvalumab	1500 mg	IV	60 minutes	Day 1 each cycle	Every 3 weeks
Followed by Maintenance					
Durvalumab	1500 mg	IV	60 minutes	Day 1 each cycle	**Every 4 weeks** Until disease progression/ unacceptable toxicity/ withdrawal of consent

Table 2: Control arm treatment

Agent (s)	Dose	Route	Duration	Schedule	Frequency
Cisplatin OR Carboplatin	75 mg/m^2 OR AUC 5	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Pemetrexed	500 mg/m^2	IV	Per institution practice	Day 1 each cycle	Every 3 weeks x 4 to 6 cycles
Followed by					
Close observation per standard of care					

Conflict of interest

Dr Sun, Dr Brown, Dr Cook, Dr Yip, Ms Ford, Ms Fitzpatrick, Ms Bricker, Ms Cummins have nothing to disclose.

Dr Kok reports grants and fees from AstraZeneca and Pfizer, she is a consultant/ advisory board member of MSD, outside the submitted work;

Dr. Forde reports grants and fees from AstraZeneca, BMS, Corvus, Novartis, Kyowa; he is a consultant/ advisory board member of Amgen, AstraZeneca, BMS, Novartis, Janssen, Iteos, Mirati, Sanofi; he is a Data Safety Monitoring Board member of Polaris, Flame, outside the submitted work;

Dr Hughes is a consultant/ advisory board member of MSD, BMS, Roche, Pfizer, AstraZeneca, Eisai, Takeda; his institution received grants from Amgen, outside the submitted work;

Dr Ramalingam reports grants and fees from Amgen, AstraZeneca, Genmab, Eisai, Lilly, Roche, Merck, Takeda and GSK; he is a Data Safety Monitoring Board member of Jansen; a member of Board for Gergia Society of Oncology and IASLC; his institution received grants from AstraZenca, Amgen, BMS, Merck, Genmab, Takeda, Advaxis and Pfizer, outside the submitted work;

Dr. Lesterhuis reports grants and fees from Douglas Pharmaceuticals, and patents relating to immune checkpoint therapy, unrelated to this study, outside the submitted work;

Dr O'Byrne has received advisory board and/or speaker bureau and/or meeting travel/registration support from BMS, MSD, LillyOncology, Boehringer-Ingelheim, Pfizer, Novartis, Roche-Genentech,Teva, Mundipharma, Astrazeneca, Janssen, Natera and TriStar. He is a board member and stock holder for Carpe Vitae Pharmaceuticals and a stock holder for RepLuca Pharmaceuticals and DGC Diagnostics and holds patents for novel therapeutics and diagnostic tests, outside the submitted work;

Dr. Pavlakis reports grants and fees from Boehringer Ingelheim, Bayer, Novartis, Pfizer, Roche, Takeda and Ipsen; he is an advisory board member of Boehringer Ingelheim, MSD, Merck, BMS, Astra Zeneca, Takeda, Pfizer and Roche; his institution received grants from Bayer, Pfizer and Roche, outside the submitted work;

Dr Brahmer reports grants and fees from AstraZeneca, BMS, Genentech/Roche, Merck, RAPT Therapeutics, Revolution Medicines, Amgen, Eli Lilly, GlaxoSmithKline, Sanofi, Regeneron; she is a Data Safety Monitoring Board member of GlaxoSmithKline, Sanofi, Janssen; she is an advisory board member of IASLC; outside the submitted work;

Dr Anagnostou's institution received grants from BMS and AstraZeneca; outside the submitted work;

Dr Stockler's institution received grants from the following competitive funding bodies: Australian National Health and Medical Research Council, Canadian Cancer Trials Group, Cancer Australia, Medical Research Future Fund of Australia; and the following pharmaceutical companies: Astellas, Amgen, Astra Zeneca, Bayer, Beigene, Bionomics, Bristol-Myers Squibb, Celgene, Medivation, Merck, Merck Sharp & Dohme, Pfizer, Roche, Sanofi, Tilray, outside the submitted work;

Dr Nowak reports grants and fees from Bayer Pharmaceuticals; Roche Pharmaceuticals; Boehringer Ingelheim; Merck Sharpe Dohme; Douglas Pharmaceuticals, Atara Biotherapeutics, Astra Zeneca (payment to institution); Pharmabcine; Trizell Ltd; Seagen; honoraria from Bristol Myers Squibb and her institution received grants from AstraZeneca and Douglas Pharmaceuticals, outside the submitted work.

Contributorship statement

Conception and design of study: Nowak, Forde, Stockler, Ramalingam, Brahmer, Pavlakis, Brown, Sun, Hughes, Kok

Conduct of study: Cummins, Ford, Fitzpatrick, Bricker,

Acquisition of data: Ford, Fitzpatrick, Bricker

Drafting the manuscript: Kok, Ford, Fitzpatrick, Bricker

Revising the manuscript critically for important intellectual content: Nowak, Forde, Stockler, Brown Hughes, Pavlakis, Cook, Lesterhuis, Yip, Cummins.

Approval of the version of the manuscript to be published: Kok, Forde, Hughes, Sun, Brown, Ramalingam, Cook, Lesterhuis, Yip, O'Byrne, Pavlakis, Brahmer, Anagnostou, Ford, Fitzpatrick, Bricker, Cummins, Stockler, Nowak.

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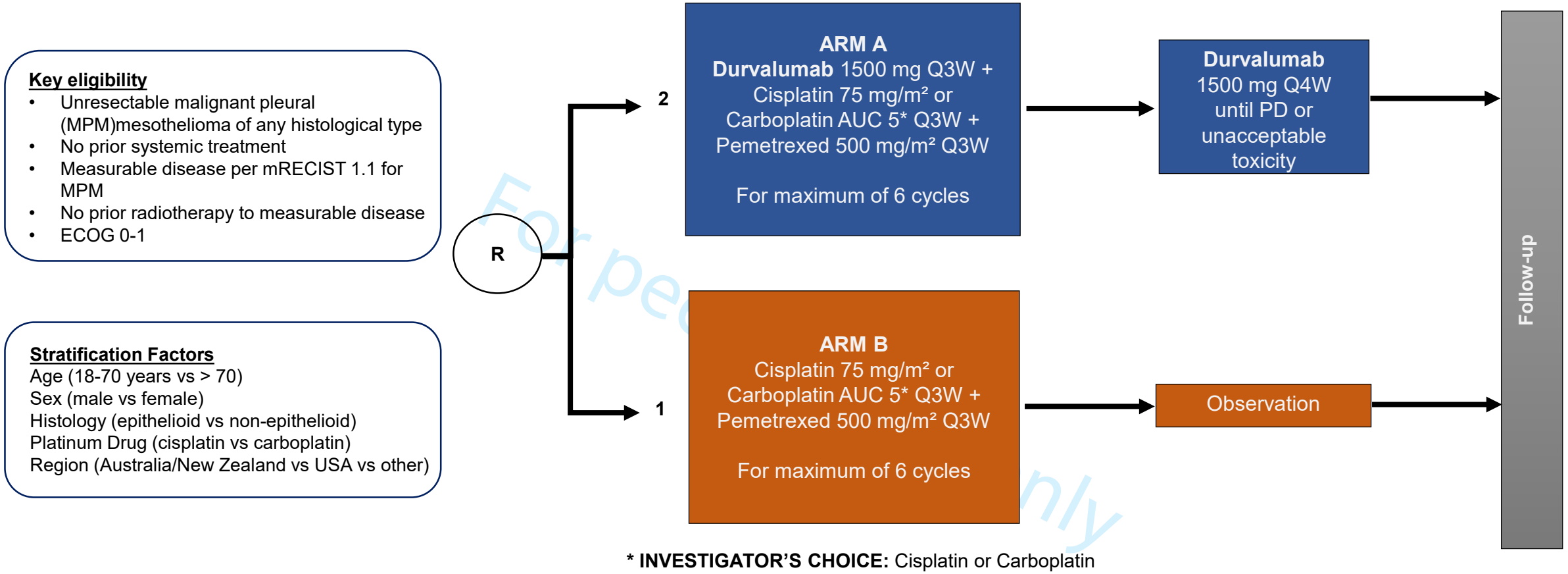

Primary endpoint: OS
Secondary endpoints: PFS, OTRR, AEs, HRQoL, healthcare resources
Tertiary endpoints: Possible prognostic/predictive biomarkers in tissue and serial blood samples: PD-L1, HLA subtypes, tumour mutation burden, genomic characteristics; validation of radiological measures of response and radiomic biomarkers

Figure 1: Study schema for DREAM3R.
Abbreviations **:** AEs, adverse events, HRQoL, health-related quality of life, HLA, human leukocyte antigen, OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Pg. 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry Pg. 52
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier All pages
Funding	4	Sources and types of financial, material, and other support Pg. 48
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors Pg. 3
	5b	Name and contact information for the trial sponsor Pg. 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities pgs, 42, 46, 48, 50, 51
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Pg. 50
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Pg. 13-20
	6b	Explanation for choice of comparators Pg. 16 and 20
Objectives	7	Specific objectives or hypotheses Pg. 21
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Pg. 24

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Pg. 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Pg. 21 - 24
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Pg. 24 - 30
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Pg. 24 - 30
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Pg. 45
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Pg. 30 - 31
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Pg. 12, 21, 46 and 47
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Pg. 33
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations pg 13, 46 and 47
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Pg. 46 and 47

Methods: Assignment of interventions (for controlled trials)

Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions Pg. 46 and 47

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned N/a
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions N/a
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how N/a
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial N/a

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Pg. 24, 37, 38, 48
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Pg. 28, 48, 49
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Pg. 48
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Pg. 46, 47
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) N/a
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Pg. 46, 47

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed pg.47

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Pg. 47
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct Pg. 41 - 44
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Pg. 49

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Pg. 47-48
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) pg. 49
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) N/a
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable N/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Pg. 48
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site N/a
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators N/a
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation N/a
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions Pg. 49
	31b	Authorship eligibility guidelines and any intended use of professional writers Pg. 49
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Pg. 49

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/a
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.